Timing and location of speech errors induced by direct cortical stimulation

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Abstract

Cortical regions supporting speech production are commonly established using neuroimaging techniques in both research and clinical settings. However, for neurosurgical purposes, structural function is routinely mapped peri-operatively using direct electrocortical stimulation. While this method is the gold standard for identification of eloquent cortical regions to preserve in neurosurgical patients, there is lack of specificity of the actual underlying cognitive processes being interrupted. To address this, we propose mapping the temporal dynamics of speech arrest across peri-sylvian cortices by quantifying the latency between stimulation and speech deficits. In doing so, we are able to distinguish functional roles (e.g., planning versus motor execution).

In this retrospective observational study, we analyzed 20 patients (12 female; age range 14-43) with refractory epilepsy who underwent continuous extra-operative intracranial EEG monitoring during an automatic speech task during clinical bed-side language mapping. Latency to speech arrest was calculated as time from stimulation onset to speech arrest onset, controlling for individuals' speech rate.

Most motor-based interruptions (87.5% of 96 instances) were in motor cortex with mid-range latencies to speech arrest (*median = 0.79 s, 95% CI = 0.55-0.92 s).* Speech arrest occurred in numerous regions, with short latencies in supramarginal gyrus (*median = 0.49 s, 95% CI = 0.41-0.61 s)*, superior temporal gyrus (*median = 0.55 s, 95% CI = 0.45-0.66 s*), and middle temporal gyrus (*median = 0.57, 95% CI = 0.43-0.79 s)*, followed by motor cortex (*median = 0.83 s, 95% CI = 0.70-1.17 s*) and inferior frontal gyrus (*median = 0.90 s, 95% CI = 0.74-0.95 s*). Nonparametric testing for speech arrest revealed that region predicted latency, $\chi^2(4) = 28.798$, $p < 0.00001$; latencies in supramarginal gyrus and in superior temporal gyrus were

shorter than in motor cortex ($D = 0.48$, $p = 0.00011$; $D = 0.38$, $p = 0.004$) and in inferior frontal gyrus ($D = 0.46$, $p < 0.00001$; $D = 0.35$, $p = 0.00095$).

Motor cortex is primarily responsible for motor-based speech interruptions. Latencies to speech arrest in supramarginal gyrus and superior temporal gyrus align with latencies to motor-based speech interruptions in motor cortex, suggesting that stimulating these regions interferes with the outgoing motor execution. The longer latencies to speech arrest in inferior frontal gyrus and in ventral regions of motor cortex suggest that stimulating these areas interrupts planning. These results implicate the ventral specialization of motor cortex for speech planning above and beyond motor execution.

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Introduction

Direct electrocortical stimulation (DES) mapping is routinely used peri-operatively in patients with epilepsy and other brain anomalies to functionally map regions critical for motor, sensory, speech and language functions.[1] Cortical stimulation results allow clinicians to map resection boundaries and avoid post-operative deficits, representing the gold standard to prevent functional impairments following epilepsy surgery.[2,3]

During DES mapping, cortex is stimulated while patients perform speech tasks. At our institution, these tasks include recitation of continuous speech, visual/auditory naming, and sentence completion,[1,4] though tasks such as continuous speech and visual naming are shared by many institutions. Hesitation, slurring, distortion, repetition, and confusion can interrupt any task.[1,2] We distinguish "motor-based arrest" and "speech arrest." Motor-based arrest occurs when stimulation impairs oral or laryngeal control to cause speech cessation; speech arrest completely interrupts speaking but is not explained by oral or laryngeal motor dysfunction.[5,6]

Based on classical[1] and recent reports[6,7] on speech arrest sites, the precentral gyrus is the most common area to induce speech arrest during DES, followed by the inferior frontal gyrus (IFG).[1,6-8] Recent probability maps converge on precentral gyrus and IFG pars opercularis as the two regions with the highest probability of inducing speech arrest.[7,8]

In these same intra-operative studies, the superior temporal gyrus (STG) is less consistently associated with speech arrest than motor cortex or IFG.[1,6,7] Clustering analyses have identified STG and the supramarginal gyrus as the fourth largest cluster after the largest clusters in precentral gyrus and pars operculus.[6] STG inconsistently induced speech arrest across patients,[8] with great variability between subjects,[7] suggesting that STG is strongly associated with speech arrest in some speakers and not others.

Other inconsistencies occur in cortical regions in which stimulation causes speech arrest. Two studies found robust speech arrest in precentral gyrus.[5,9] However, one of these studies found sparse speech arrest in IFG (4% chance of speech arrest), STG (0%), and supramarginal gyrus (8%).[9] The other study found sparse speech arrest in IFG or STG, and none in supramarginal gyrus.[5] Some inconsistencies likely reflect clinical differences in mapping procedures (e.g., differences between intra-operative DES[1,6-9] versus extra-operative DES mapping[5]) and differences in coverage for epilepsy[1,5,7,8] versus tumor mappings.[6,8,9] Differences in stimulation

parameters, particularly the electrical current intensity, within and across sites may also contribute to inconsistent prior findings.

Past studies reported spatial location of speech arrest, but individual variability and inconsistencies across studies did not explore timing or functional roles of regions. To address this, we reported the timing of how long it takes stimulation to induce speech arrest in five peri-sylvian cortical regions during extra-operative DES mapping. To our knowledge, this is the first report of the timing of speech arrest following DES, providing a window into the functional architecture and neural timing underlying speech production. One prior study employing repetitive transcranial magnetic stimulation (rTMS) reported that the timing from stimulation onset to speech arrest was 1±3s.[10] Using DES during extra-operative clinical mapping, our data set offers unprecedented spatial and temporal precision to distinguish latencies in different cortical regions. Mapping out latencies for inducing speech arrest across cortex could identify which phase in the speech production process various types of interruptions occurred.

We assess whether latencies from stimulation onset to speech arrest during a continuous speaking task differ across five peri-sylvian cortical regions: sensorimotor cortex (which we define anatomically to include both precentral and postcentral gyri), IFG, STG, supramarginal gyrus, and middle temporal gyrus (MTG). Speech production models highlight premotor cortex in executing motor programs and IFG in linking phonology to speech motor control.[11,12] During word repetition, neural representations are forwarded from STG to IFG, where they link to articulatory representations, which are subsequently implemented by the articulators via motor cortex. Since IFG activity precedes speech production[13-15] by approximately 250 milliseconds,[13] we hypothesized that stimulation in motor cortex would more rapidly interrupt speech than IFG stimulation. We predicted that motor cortex stimulation interrupts mid-trajectory in the motor execution phase of speech production, with short latencies to speech arrest. Conversely, we predicted that IFG stimulation would lead to interruptions to the outgoing plan, which should only affect future speech, resulting in relatively long latencies from stimulation to speech arrest. These hypotheses are consistent with motor cortex and inferior frontal gyrus (IFG) being the most likely cortical sites to elicit speech arrest, as well as their putative functional roles in speech production models.[11,13,16,17]

Materials and methods

Subject selection

All the patients at NYU Langone Hospital who underwent DES mapping who had precise synchronization of EEG with audio in the clinical system were considered for inclusion in this retrospective observational study. This comprised fifty patients who were implanted from September 2018 through September 2021, beginning from when data were available in the Natus® Neuroworks® EEG system, providing a software development kit (SDK) to synchronize audio and EEG with high fidelity. All patients were implanted with subdural and depth electrodes (AdTech Medical Instrument Corp.) and underwent bedside extra-operative DES mapping to identify eloquent (motor, language) cortex prior to surgical resection of epileptogenic tissue as part of their routine clinical care. A total of 20 patients (12 females; mean age 27.7, SD = 10.46, age range = 14-43; 1 right, 19 left hemisphere coverage; mean age of diagnosis 12.4, SD = 8.0) were reported to have speech interruptions that were labeled as motor hits or as language hits (including "speech arrest"), which is further defined in a later section. Electrode coverage typically comprised grids (8x8 contact), strips over cortex (4-8 electrodes), and depth electrodes (≤8 electrodes). Surface reconstructions, electrode localization, and MNI coordinates were extracted by aligning a postoperative brain MRI to the preoperative brain MRI using previously published methods.[18] See plots of electrode coverage for all patients in Supplementary Fig. 1.

Informed consent

All patients gave informed consent to participate in research and for audio/video to be recorded and analyzed, as approved by the New York University Langone Health Institutional Review Board. Table 1 lists all patients considered for this analysis.

Clinical battery

As part of the battery of clinical tasks routinely administered to elicit language,[19] the current focus is on the continuous speech elicited during counting or reciting days of the week, months of the year, or the Pledge of Allegiance. Though not analyzed in the present study, patients also completed higher-level tasks eliciting visual and auditory naming and auditory comprehension

with the goal of capturing multiple modalities of language processing, as in previous.[20] Following clinical protocol,[19] stimulation was presented to electrode pairs using a NicoletOne Cortical Stimulator which typically involved bipolar contiguous contacts delivering a low-intensity current (0.5-6 mA) that was gradually increased (maximum 15 mA) across multiple trials to find the threshold at which cortical spread (afterdischarges) did not occur and a behavioral deficit was observed. Current was delivered with a biphasic pulse width of 300-500 μs at a pulse rate of 50 Hz with a train duration from 3-5 s. Channels were inspected by an epileptologist and those eliciting afterdischarges were flagged.

Following clinical protocol at NYU Langone, for each electrode pair, each patient began counting as their voice was recorded using an external microphone connected to the clinical audio/video system. Stimulation was delivered in selected intervals during continuous speech, beginning at the lowest intensity current level and gradually increasing within established thresholds suntil a behavioral deficit was observed. Although there were multiple stimulation trials within a sequence that were delivered at different stimulation intensity levels, only the level for the final trial was documented following clinical protocol (see results and discussion). Once a behavioral deficit was observed, stimulation was repeated while the patient continued the same task until the same deficit occurred on at least two out of three trials. When there was no behavioral deficit, the target electrode pair was considered "cleared." If the site was found to be a motor hit (see next paragraph for how this was determined), then stimulation mapping was complete for that electrode pair. If the site was determined to be a language hit, then a higher-level continuous speaking task was elicited (e.g., days of the week, months of the year, Pledge of Allegiance). We acknowledge that the first three tasks (counting, reciting days/months) can be considered more automatic than that in the Pledge of Allegiance, which would be considered to involve more propositional language. However, this task was only used to elicit speech from those who had it memorized, suggesting that it was produced with a high degree of automaticity.

Based on the epileptologist reports available in the clinical system, individual electrodes were labeled as motor hits or as language hits. This determination was made by ruling out whether each speech interruption was caused by motor interference. That is, a site was determined to be a motor hit if a part of the patient's body reliably moved during rapid repeated production (i.e., diadochokinesis) of the nonspeech syllables "pa," "ta", "ka", or "la". Interruptions were only considered motor hits if the motor activity directly interfered with speech output. "Speech arrest" is defined as the complete interruption of the ability to continue speaking that is not

directly explained by oral or laryngeal movements.[5,6] As such, only those language hits involving complete cessation of speech were subcategorized as speech arrest.

Measurement

Using Neuroworks, we viewed the video recordings of DES bedside mapping for all 20 patients. Time stamps for the onset of stimulation for all speech interruptions during continuous speaking were noted in conjunction with dipole electrode labels. Although our focus is on speech interruptions independent of whether they are due to motor causes, we liberally included in the initial data set all trials involving a noticeable change in speech output coinciding with stimulation.

To obtain precise recordings of stimulation intervals, we read in proprietary Natus files (.ERD, .ETC., .STC, .SNC) and extracted the EEG signal from the first in each pair of target electrodes (dipole 1) using custom Matlab code based on the SDK provided by Natus.[21] For each patient, we read in the Natus video file and extracted the time-synced audio signal from the bedside recording (synchronization was based on the associated synchronization files used by Natus, including .ETC, .STC, .SNC, and .VTC formats). For each patient and unique target electrode (dipole 1), we extracted a stereo audio recording including stimulation signals (channel 1) and time-synced audio (channel 2).

Using Praat software[22] for acoustic analysis, we generated time-synced TextGrids for each extracted stereo audio file. Fig. 1 (panel A) shows an example audio signal and aligned annotated TextGrid, including one speech arrest event. First, a window was created around each speech interruption, which encompassed utterances leading up to and following the interruption up until the next stimulation interval began or the clinician intervened. Within those windows, a tier ("word") was used to label the onset and offset of each word in each target sequence. On a second tier ("stim"), we annotated the precise timing of stimulation, which was visible as each interval of non-zero amplitude in the EEG signal from channel 1. A final tier ("arrest") was used to mark the moment at which speech interruptions occurred, including complete cessation of speech (marked with an asterisk). Also coded on the "arrest tier," symbols denote whether the patient was cut off from continuing speaking (+/-) and whether the patient could continue where they left off (c) following the speech interruption. Though not reported presently, additional observed changes in the speech output were noted on this tier, including slowed speech, pauses, non-target vocalizations, perseverations or skips

in the sequence, changes in vocal quality or volume, and speech aberrations classified as dysarthric or apraxic.

The primary outcome measure is latency from stimulation onset to speech arrest. One limit of analyzing speech arrest timing is ambiguity of interruption onset, even in continuous speech. In contrast to speech degradations that can be marked in the audio, speech arrest onset corresponds with signal loss, which occurs somewhere between the end of the last word spoken and the time when the next word would have been spoken at the same rate. As true latencies cannot be directly measured, we used this method to approximate them. Raw latencies were calculated as the time from the onset of stimulation to the onset of speech arrest (see Fig. 1, panel A). Thus, negative latencies are possible because speech arrest is marked at the end of the last word that was spoken, which could occur before stimulation onset even though the true speech arrest would be prior to the next expected word in the sequence. To account for pre-stimulation speech rate within and between patients, we adjusted raw latencies by adding the average duration between all words prior to stimulation onset in each trial (and between phrases for the Pledge of Allegiance. Making these adjustments to the raw latencies eliminated many negative latencies while providing the closest possible latency estimations.

Timings were extracted from the measured Praat TextGrid boundaries and read into R[23] using RStudio. Each electrode label was matched with both the name of the corresponding brain region based on the subject's own pre-operative MRI and the standardized MNI coordinates. Each speech interruption was matched with the label "motor hit" or "language hit" based on the clinician reports. As previously described, electrode pairs determined to be language hits were also considered speech arrest hits if the clinical report listed that electrode pair as a hit for speech arrest. As multiple trials were elicited for each electrode pair, only those trials with a hard cessation of speech were labeled as speech arrest.

Analysis

Across the 20 patients, there were 360 trials labeled as motor hits or speech arrest hits by the clinical team. Latencies greater than two standard deviations from the mean of latencies (n = 6) and trials in which there was no hard cessation of speech (n = 80) were removed, leaving 274 trials for consideration. Because our broad regions of interest were sensorimotor cortex, IFG, STG, supramarginal gyrus, and MTG, those trials for which stimulation was applied outside these areas (n = 23) were removed for statistical analyses, but these trials were

preserved in all brain plots. Among these exclusions were two trials from one patient for which a depth electrode spanned precentral gyrus and white cerebral matter. All remaining trials comprised two grid electrodes on cortex with at least one electrode in a region of interest. After removal of trials from other regions, those trials in which stimulation induced afterdischarges (n = 82) were flagged for future exclusion (see results section). Thus, the final data set for analysis included 169 unique trials in 16 patients. Of the 274 trials analyzed, only nine trials were elicited using the Pledge of Allegiance; following data cleanup, only two of these trials were included in the final statistical analysis. See table 2 for complete electrode counts in each region from all 274 trials considered for analysis, pooled across trials that induced motor-based and speech arrest hits. The central column includes electrode counts for trials on which stimulation did not induce afterdischarges (n = 185); the right column includes electrode counts for trials on which stimulation induced afterdischarges (n = 89). The top section includes electrode counts in the five broad regions of interest, where the top central section includes the electrodes for which stimulation did not induce afterdischarges and that were included in the final analyses (n = 165). The histograms in Fig. 1 show the distributions of latencies for all trials (panel B) and for the subset of trials that did not induce afterdischarges (panel C).

We first used *t*-tests to compare locations and latencies for motor hits versus speech arrest hits, and to compare latencies for trials with versus without afterdischarges. Controlling for stimulation parameters, we then determined whether region (sensorimotor cortex, IFG, STG, supramarginal gyrus, MTG) predicts adjusted latency from stimulation onset to speech arrest using a non-parametric Kruskal-Wallis test. To determine whether density distributions were different between the five broad regions, we conducted post-hoc Kolmogorov–Smirnov tests between each pair of regions. Finally, latency patterns were visualized on brain regions across cortex and compared using smoothed density plots.

Data availability

Anonymized data will be shared upon request.

Results

Motor versus speech arrest hits in three broad regions

In order to understand the spatial topography of speech arrest, we first analyzed the spatial distribution of motor-based hits versus speech arrest hits in order to verify locations (Fig. 2). We found that the main regions implicated included our broad regions of interest: sensorimotor cortex, IFG, STG, and supramarginal gyrus, in addition to MTG. Regardless of type of arrest elicited, latencies (i.e., the "adjusted latencies" described in the methods section) for motor hits were not different from latencies for speech arrest hits across all trials including afterdischarges, $t(249) = 0.770$, $p = 0.442$ (Fig. 2A). Upon removal of all trials with afterdischarges, we still found no difference between motor-based versus speech arrest hits despite there being fewer trials, $t(167) = 1.48$, $p = 0.141$ (Fig. 2B).

Comparing trials with and without afterdischarges

In order to rule out the effect of epileptic activity, we removed all trials with afterdischarges from subsequent analyses. Comparison of latencies for all motor-based and speech arrest hits in trials with and without afterdischarges provides further rationale for this exclusion (Fig. 3). That is, trials with afterdischarges had longer latencies than trials without afterdischarges for motor-based hits, $t(63) = -2.06$, $p = 0.0437$ (Fig. 3A) and for speech arrest hits, $t(184) = -4.97$, $p < 0.0001$ (Fig. 3B).

Regional differences in latency

Before comparing regional differences in latency, we considered distributions of motor hits and speech arrest hits in each cortical region (Fig. 4A). The majority (87.5% of 96 instances) of motor-based hits were in sensorimotor cortex, whereas speech arrest hits were relatively more spread out across cortex. Within sensorimotor cortex, there were relatively more motor hits (75%) than speech arrest hits (25%), but there were substantially more speech arrest hits relative to the number of motor hits within supramarginal gyrus (96.8%), STG (94.5%); MTG (100%), and IFG (89%). Within sensorimotor cortex, motor-based hits tended to span both dorsal and ventral regions, whereas speech arrest hits tended to be isolated to ventral regions (see discussion).

Including all trials of speech arrest, we then tested statistically whether latencies in each broad cortical region differed (Fig. 4B). A nonparametric Kruskal-Wallis test indicated that variances between the five broad cortical regions were significantly different from one another, $\chi^2(4) = 28.798$, $p < 0.00001$. To determine whether stimulation parameters influenced latency differently for each region, we ran a linear mixed effects regression model predicting latency on a subset of the data including only the final trial in each stimulation sequence, so that the highest electrical stimulation level correctly corresponded with the final trial in that sequence. We predicted latency from region, stimulation level (in mA), and the interaction between these two predictors, while including a random intercept for patient. Region was a significant predictor of latency [F(4, 81.872) = 2.759, p = 0.0331]; neither stimulation level [F(4, 81.188) = 1.359, p = 0.247] nor the interaction between region and stimulation level [F(4, 81.609) = 1.171, p = 0.330] significantly predicted latency. Ten post-hoc Kolmogorov–Smirnov tests indicated that at the Bonferroni corrected p-value of 0.005, latencies in supramarginal gyrus were significantly shorter than in Sensorimotor Cortex ($D = 0.48$, $p = 0.00011$) and in IFG ($D = 0.46$, $p < 0.00001$), and latencies in STG were significantly shorter than in Sensorimotor Cortex ($D = 0.38$, $p = 0.004$) and in IFG ($D = 0.35$, $p = 0.00095$). Latencies in MTG were shorter than in Sensorimotor Cortex ($D = 0.39$, $p = 0.024$) and in IFG ($D = 0.36$, $p = 0.013$), but these differences were only at the uncorrected p-value threshold of 0.05. Latencies between all other regions were not significantly different from one another (Sensorimotor Cortex versus IFG [$D = 0.28$, $p = 0.086$]; supramarginal gyrus versus STG [$D = 0.14$, $p = 0.44$]; supramarginal gyrus versus MTG [$D = 0.15$, $p = 0.70$], STG versus MTG [$D = 0.10$, $p = 0.95$].

Temporal map of latencies across cortex

Finally, we analyzed the temporal dynamics of latencies to speech arrest across cortex in four time bins (Fig. 5A). Latencies less than 0.5 seconds were associated with a high density of speech arrest following stimulation in supramarginal gyrus and STG. At latencies from 0.5-1 second, the density of speech arrest in STG faded while the density in IFG increased. For latencies greater than 1 second, there was relatively high density of speech arrest in IFG and possibly also in STG.

We also analyzed the temporal dynamics of speech arrest across cortex by looking at distributions of latencies in the broad regions of interest, with the cortical locations and distribution of latencies of motor hits in sensorimotor cortex also plotted for reference (Fig.

5B). Looking at speech arrest patterns across the regions (Fig. 5C), there are early peaks in temporoparietal areas, including supramarginal gyrus at 0.46 seconds (median = 0.49, 95% CI = 0.41-0.61), STG at 0.51 seconds (median = 0.55, 95% CI = 0.45- 0.66), and MTG at 0.54 seconds (median = 0.57, 95% CI = 0.43-0.79). Later peaks occur in sensorimotor cortex at 0.72 seconds (median = 0.83, 95% CI = 0.70-1.17) and in IFG at 0.95 seconds (median = 0.90, 95% CI = 0.74-0.95). In contrast to the later peaks for speech arrest in sensorimotor cortex, motor hits in sensorimotor cortex show an early peak at 0.47 seconds (median = 0.79, 95% CI = 0.55-0.92). Additionally, Fig. 5B shows how motor-based hits span sensorimotor cortex whereas speech arrest hits in this region tend to be ventrally located.

Discussion

By reporting on the timing of stimulation to speech arrest involving the spatial precision of electrocorticography, we observed that shorter latencies were associated with motor-based speech interruptions across sensorimotor cortex and with speech arrest in supramarginal gyrus and STG. In contrast, longer latencies were associated with speech arrest in ventral portions of sensorimotor cortex and in IFG. These results suggest that stimulation in specific neural regions interrupts disparate processes of speech motor control with execution and planning occurring in distinct areas within sensorimotor cortex.

The goal of this study was to characterize patterns of region-specific latency from stimulation onset to motor-based speech interruptions and to speech arrest in five peri-sylvian cortical regions. Trials with afterdischarges were excluded from analyses because epileptic activity could not be ruled out in these trials and because speech arrest latencies that induced afterdischarges were significantly longer than trials that did not induce afterdischarges. In summary, there were relatively more motor hits in sensorimotor regions than in other cortical areas, while there were more speech arrest hits than motor hits in the other cortical areas, including supramarginal gyrus, STG, MTG, and IFG. Latencies for electrodes that were labeled as motor hits were not different than latencies for speech arrest hits. For speech arrest, the earliest latencies were in supramarginal gyrus and STG, and latencies in these regions (and in MTG to a lesser extent) were significantly shorter than latencies in both sensorimotor cortex and IFG. Latencies for speech arrest within supramarginal gyrus, STG, and MTG were not different from one another; latencies in sensorimotor cortex and IFG were also not different from one another, as predicted.

We had hypothesized that stimulation in sensorimotor cortex would interrupt motor execution midstream leading to the prediction that stimulation within this region would have the shortest latencies; conversely, we had hypothesized that IFG would interrupt motor planning leading to the prediction that this region would have relatively longer latencies. We were surprised to find that the earliest peak latencies for speech arrest were in supramarginal gyrus (0.46 s) and STG (0.51 s), and that latencies in these regions were significantly shorter than latencies in sensorimotor cortex (peak at 0.72 s) and in IFG (peak at 0.95 s). The early peak latencies in supramarginal gyrus and STG for speech arrest aligned with the early peak latency for motor hits in sensorimotor cortex (0.47 s), suggesting that temporoparietal and sensorimotor areas may be involved with interruptions in motor execution. In contrast, the relatively long latencies for speech arrest in sensorimotor cortex and in IFG suggest that there was interruption to planning processes. Within sensorimotor cortex, latencies to motor-based speech arrest occurred relatively early and within temporoparietal areas as well as areas throughout precentral and postcentral gyri. However, latencies to events labeled as speech arrest occurred relatively late and within IFG and more ventrally located parts of sensorimotor cortex. This novel finding suggests that motor execution and planning processes occur in distinct areas within sensorimotor cortex.

What stands out in this study is the surprisingly short latencies to speech arrest found in supramarginal gyrus and STG. We considered two potential mechanisms for these quick interruptions in temporoparietal areas. First, stimulation could interfere with lexical access when speaking, as both speech arrest and anomia occur within supramarginal and STG sites.[6] However, when reviewing the sites for which anomia was elicited in our data set, this hypothesis was not supported because the hits for speech arrest in supramarginal gyrus and STG were not also hits for anomia. Instead, our data support a self-monitoring hypothesis in which stimulation causes an interruption within the auditory feedback loop, thus interrupting real-time feedback-based updates to the outgoing motor plan. This claim is supported by our finding that latencies for speech arrest in STG were comparable to latencies to motor-based speech interruptions in sensorimotor cortex. This claim is also supported by research linking deficits in auditory-verbal short-term memory to supramarginal gyrus.[24] Furthermore, multiple studies have shown efference copy in temporal regions,[25,26] a process by which motor regions inform auditory areas of planned outgoing motor commands. Thus, this link between motor and auditory areas might explain the similar latencies observed between sensorimotor cortex and STG.

Our data corroborate past findings from multiple studies reporting speech arrest in two main cortical regions, including motor cortex and IFG.[1,6-8] As the most consistently reported site for speech arrest is premotor cortex, our study highlights how most of the speech interruptions in this region were not speech arrest per se because they were determined to be motoric in nature. Our findings also reveal robust speech arrest in IFG, in contrast to studies showing sparse speech arrest in this region,[5,9] but compatible with other reports.[6-8,27] We also showed robust speech arrest in temporoparietal areas, in contrast to past reports indicating sparse and highly variable speech arrest in supramarginal gyrus[6] and in STG.[5-7,9] As reported in table 2, most speech interruptions occurred in our five regions of interest across the sixteen patients in included in the analysis, suggesting that we have provided a comprehensive analysis of speech arrest across cortex.

There are some limitations to the present study that are worth mentioning. The main limitation is electrode coverage. Coverage was dictated by clinical necessity and although our data set collectively included extensive coverage of sensorimotor cortex, IFG, supramarginal gyrus, STG, and MTG, some patients did not have coverage of all five regions of interest. In addition, only one patient who was initially considered but was not included in the final analyses had coverage over the right hemisphere, which limits our capacity to answer any questions related to lateralization. A second limitation is that we could not control for stimulation level for all trials in our data set because the documented stimulation level corresponded only to the final trial in each stimulation sequence. However, for the subset of our data that included only these final trials, stimulation level did not predict latency, nor did it correspond with latencies in region-specific manner. Although unlikely that stimulation level affected latency differently within different cortical regions, future research should test this directly by documenting stimulation level for each trial within a stimulation sequence.

Most of the previous studies reporting cortical sites for inducing speech arrest were intra-operative and therefore had limited cortical coverage.[1,6-9] Our study complements a growing number of reports examining speech arrest mapped extra-operatively.[5,28] We believe that the broader cortical coverage enabled by extra-operative DES mapping lends strong support to the robustness of the spatial patterns observed in our data set. Furthermore, electrode diameters and inter-electrode distances used during each approach differ in an important way. Cortical grids used in extra-operative mapping contain bipolar electrodes that are 2.4 millimeters in diameter with ten-millimeter inter-electrode distances, whereas cortical probes used intra-operatively contain electrodes that are one millimeter in diameter with five-millimeter inter-

electrode distances.[29] These differences in DES mapping approaches suggest that even though extra-operative mapping has broader coverage across cortex, intra-operative mapping could have more detailed spatial sampling within the probed cortical regions. This suggests that arriving at a consensus of insights derived through both approaches will be important to understanding the spatial and temporal dynamics of speech arrest across cortex.

This study provides a unique window into the functional architecture and neural timing of speech arrest by providing a map of how long it takes stimulation to induce speech arrest across cortical regions. Our study corroborates past reports of robust speech arrest in premotor cortex and IFG while lending strong support to supramarginal gyrus, STG, and MTG being robust sites for speech arrest. Analyses of timing from stimulation onset to speech arrest revealed that supramarginal gyrus and STG had the shortest latencies, comparable to those from motor-based interruptions induced broadly in sensorimotor cortex. In contrast, speech arrest induced in ventral parts of premotor cortex and in IFG had relatively long latencies. These results support a speech production framework in which longer latencies are associated with speech motor planning, whereas shorter latencies are associated with motor execution, which encompasses real-time feedback-based updates to motor execution. Clinically, our results suggest that stimulation in premotor cortex generally interrupts motor execution, but that stimulation in ventral premotor regions as well as in IFG interrupts planning processes.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1. Measurement and distributions of adjusted time elapsed since stimulation onset, controlling for trials with afterdischarges. (A) In Praat acoustic analysis software, we visualized the stimulation intervals (channel 1) and the audio signal (channel 2). Based on channel 1, we annotated precise onset and offset of stimulation in a tier labeled "stim." Within each trial in channel 2, we annotated each word interval in a tier labeled "word," and the exact timing of speech arrest events in a tier labeled "arrest." Symbols on the "arrest" tier denote speech arrest (*), that the patient was able to continue speaking after the initial interruption (+), and that they continued counting right where they left off (c). Raw latencies, as shown with the red arrow, were calculated as the time (in seconds) elapsed between stimulation onset (from the "stim" tier) and the onset of speech arrest (from the "arrest" tier). Adjusted latencies were derived by adding to the raw latencies the average duration between all words prior to stimulation onset in each trial sequence. **(B)** Distribution of all adjusted latencies, including trials with afterdischarges. **(C)** Distribution of all adjusted latencies, excluding trials with afterdischarges.

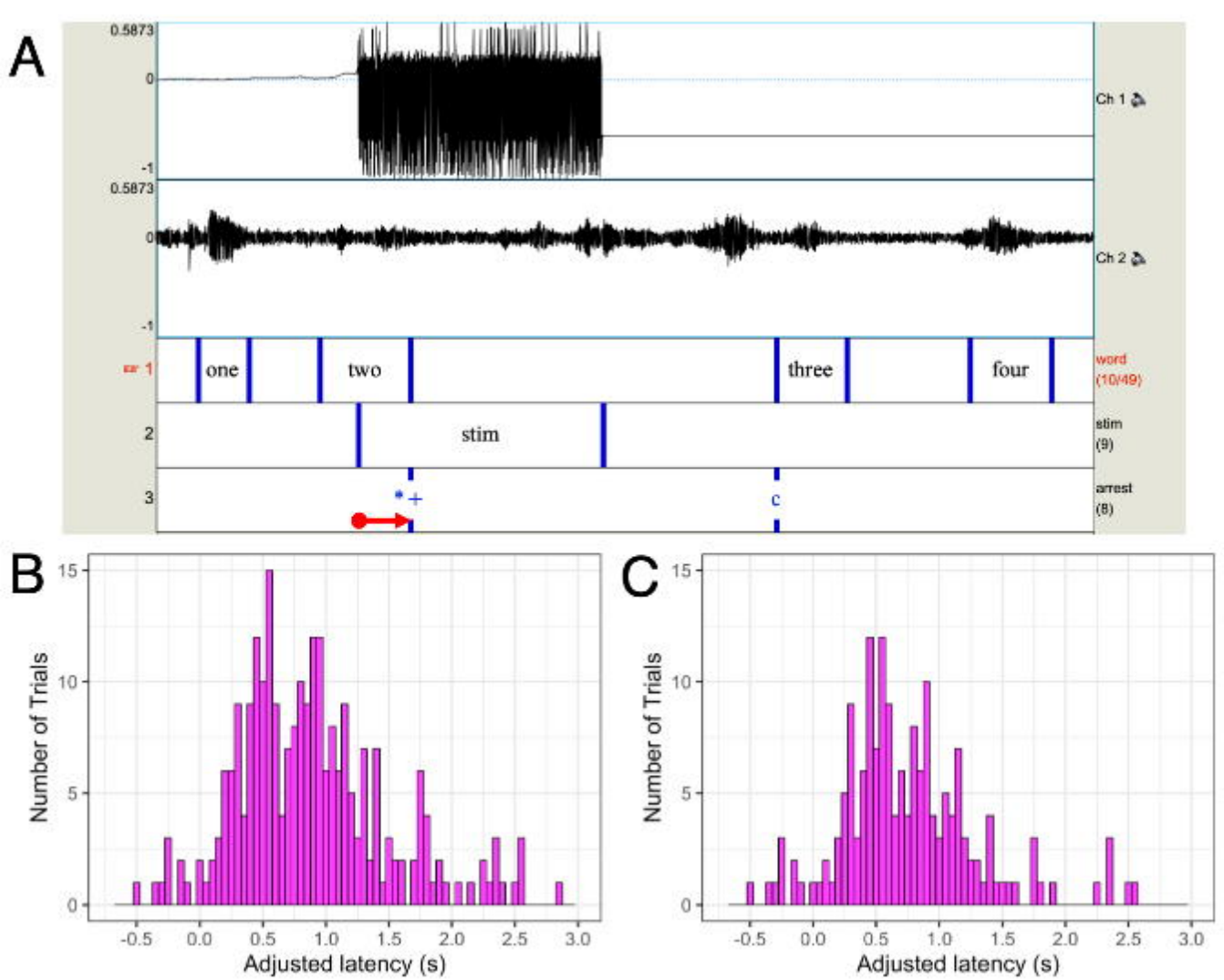
Figure 2. Cortical locations and distributions of latencies for all motor and speech arrest hits, controlling for trials with afterdischarges. (A) Brain plots of cortical locations (top) and histograms and density plots of latencies (bottom) for all motor hits (left) and speech arrest hits (right) in all trials including those with and without afterdischarges. The dashed lines in the histograms indicate the mean, which is labeled with the standard error of the mean. Asterisks indicate trials where afterdischarges were elicited while circles indicate trials in which there were no afterdischarges. **(B)** Same as panel A, but only those trials excluding afterdischarges are shown. Circles indicate electrodes through which the current was flowing in (dipole 1) while the triangles indicate electrodes through which the current was flowing out (dipole 2).

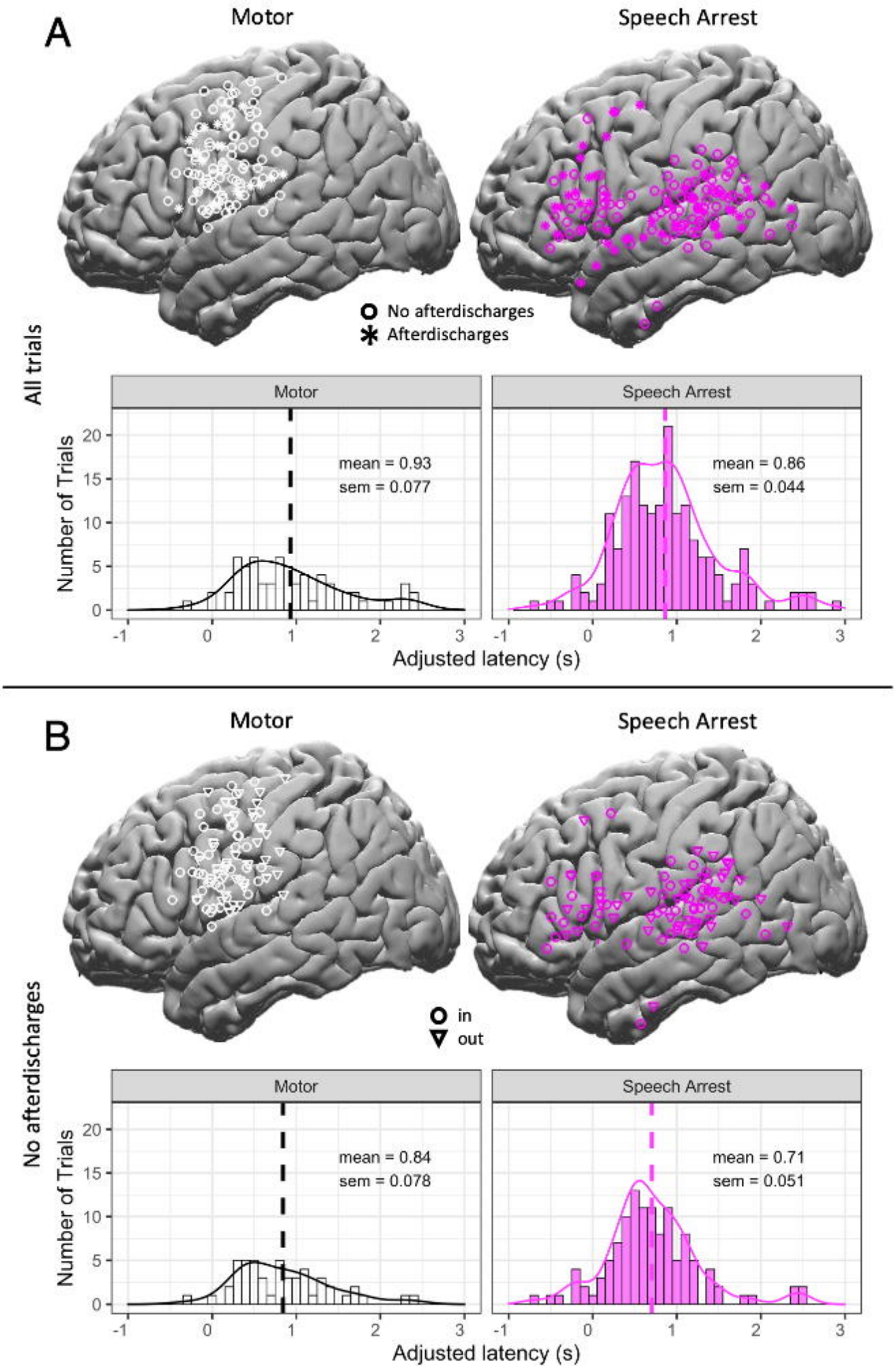
Figure 3: Distributions of latencies for all motor hits, controlling for trials with afterdischarges. (A) Histograms and density plots of latencies for all motor hits, including

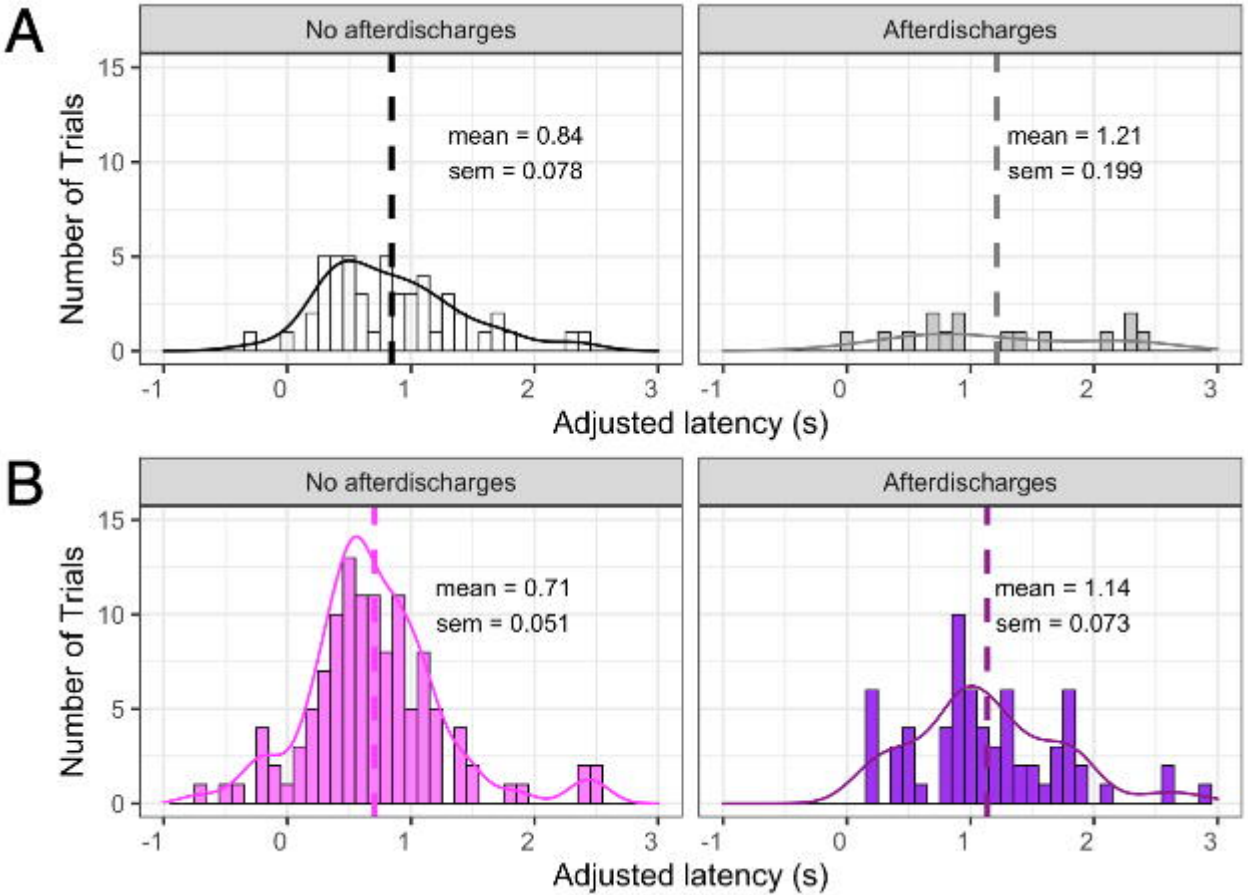
trials with no afterdischarges (left) and trials with afterdischarges (right). Dashed lines indicate the mean, which is labeled with the standard error of the mean. **(B)** Same as panel A, but only speech arrest hits are shown.

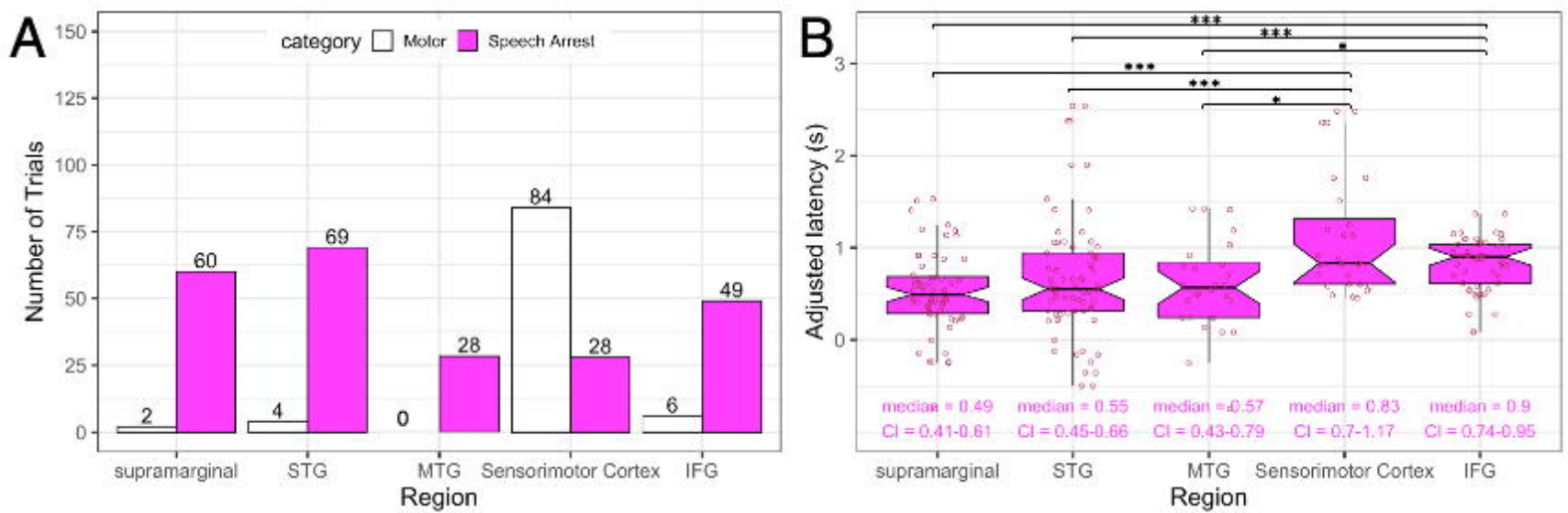
Figure 4: Summary of motor hits and speech arrest hits in each cortical region. Caption. **(A)** Distribution of motor hits and speech arrest hits in each cortical region, with the number of electrodes in each group labeled. **(B)** Boxplots of latencies for each cortical region, with individual data points shown and labels indicating median latency with 95% confidence intervals for the median labeled and shown as notches. Three asterisks indicate significant post-hoc tests at the Bonferroni-corrected $p = 0.005$ level; single asterisks indicate marginal significance at the 0.05 level.

Figure 5*:* Cortical locations and distributions of speech arrest hits relative to motor hits. **(A)** Map of the density of speech arrest hits across cortex in four time bins of adjusted latency. **(B)** Cortical locations and distributions of adjusted latencies for all speech arrest hits within each region, and for all motor hits in sensorimotor cortex. All electrodes are based on within-subject anatomy, which may differ in plotting location following normalization to Montreal Neurological Institute (MNI) coordinates. **(C)** Smoothed distributions of adjusted latencies, including speech arrest hits in supramarginal gyrus (purple), STG (red), MTG (yellow), IFG (green) and sensorimotor cortex (blue), and as a comparison, the motor hits in sensorimotor cortex (gray dashed distribution). Density plots are scaled based on the number of electrodes in each distribution and a 0.15 second bin width. Dashed vertical lines mark the peak of each smoothed distribution line, with labeled peak values.


A
0.5873
0
-1
Ch 1
0.5873
0
-1
Ch 2
1
one
two
three
four
word
(10/49)
2
stim
stim
(9)
3
c
arrest
(8)
B
Number of Trials
Adjusted latency (s)
C
Number of Trials
Adjusted latency (s)


A
Motor
Speech Arrest
No afterdischarges
Afterdischarges
All trials
Motor
Speech Arrest
mean = 0.93
sem = 0.077
mean = 0.86
sem = 0.044
Number of Trials
Adjusted latency (s)
B
Motor
Speech Arrest
in
out
No afterdischarges
Motor
Speech Arrest
mean = 0.84
sem = 0.078
mean = 0.71
sem = 0.051
Number of Trials
Adjusted latency (s)


A
No afterdischarges
Afterdischarges
mean = 0.84
sem = 0.078
mean = 1.21
sem = 0.199
Number of Trials
Adjusted latency (s)
B
No afterdischarges
Afterdischarges
mean = 0.71
sem = 0.051
mean = 1.14
sem = 0.073
Number of Trials
Adjusted latency (s)


A
category
Motor
Speech Arrest
Number of Trials
150
125
100
75
50
25
0
2
60
4
69
0
28
84
28
6
49
supramarginal
STG
MTG
Sensorimotor Cortex
IFG
Region
B
Adjusted latency (s)
3
2
1
0
***
***
***
***
*
*
median = 0.49
CI = 0.41-0.61
median = 0.55
CI = 0.45-0.66
median = 0.57
CI = 0.43-0.79
median = 0.83
CI = 0.7-1.17
median = 0.9
CI = 0.74-0.95
supramarginal
STG
MTG
Sensorimotor Cortex
IFG
Region

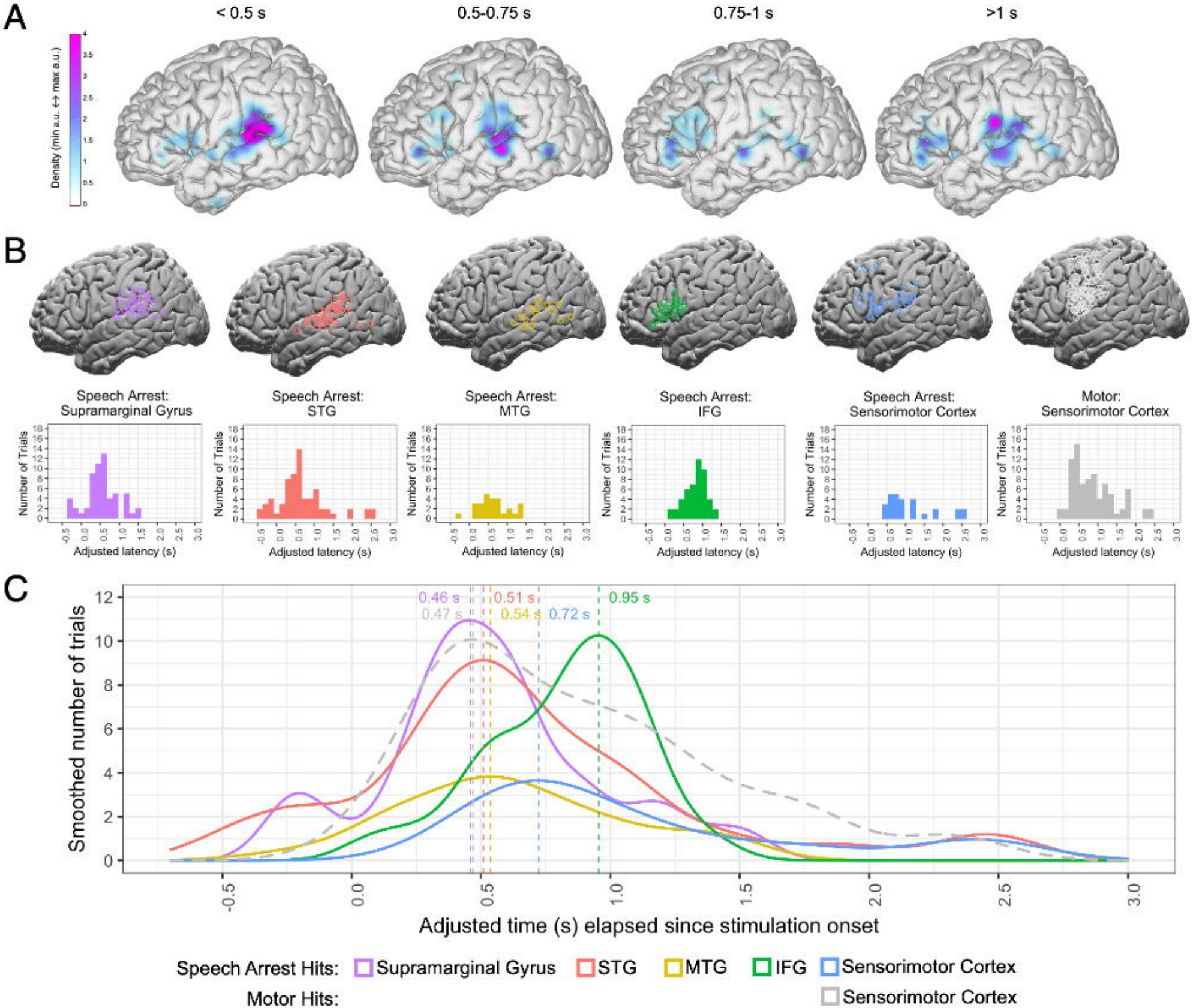

A
< 0.5 s
0.5-0.75 s
0.75-1 s
>1 s
Density (min a.u. ↔ max a.u.)
B
Speech Arrest: Supramarginal Gyrus
Speech Arrest: STG
Speech Arrest: MTG
Speech Arrest: IFG
Speech Arrest: Sensorimotor Cortex
Motor: Sensorimotor Cortex
Number of Trials
Adjusted latency (s)
C
0.46 s
0.47 s
0.51 s
0.54 s
0.72 s
0.95 s
Smoothed number of trials
Adjusted time (s) elapsed since stimulation onset
Speech Arrest Hits: Supramarginal Gyrus STG MTG IFG Sensorimotor Cortex
Motor Hits: Sensorimotor Cortex

Table 1. Patient characteristics, including anonymized ID, handedness, languages spoken ordered by proficiency, seizure focus, verbal skill, and language/memory lateralization for all twenty originally included patients

ID	Hand	Language	Seizure focus per electrocorticographic mapping	VCI	Wada test
1	R	English	Left mesial temporal lobe (mesial temporal pole, parahippocampal gyrus, anterior and posterior mesial temporal)	102	Left language, left memory 11/12, right memory 7/12; right hemispheric memory dysfunction
2	R	English	Left anteromesial temporal lobe	102	Bilateral language, left memory 11/12, right memory 12/12: intact memory bilaterally
3	R	English	Left parietal lobe epilepsy and psychogenic nonepileptic seizures	126	NA
4	R	English	Left frontal lobe (arising from focal cortical dysplasia)	81	NA
5	R	English	Left posterior insula and periopercular area	100	Left language, left memory 12/12, right memory 12/12; intact memory bilaterally
6[a]	*R*	*English*	*Right mesial temporal lobe epilepsy; habitual seizures arose from the right hippocampus. (Subclinical seizures were also captured arising from the right occipital lobe)*	*70*	*NA*
7	R	English	left posterior inferior temporal cortex with a broad field of onset	98	Left language, left memory 10/12, right memory 12/12; intact memory bilaterally
8	R	English	Left mesial temporal lobe (mesial temporal pole, parahippocampal gyrus, anterior and posterior mesial temporal)	96	Left language, left memory 10/12 and right memory 9/12; intact memory bilaterally
9	R	English	Left frontal operculum	136	Left language, left memory 12/12, right memory 11/12; intact memory bilaterally
10[a]	*R*	*English*	*left middle frontal gyrus, known malformation of cortical development*	-	*NA*
11	R	English; Spanish	Left temporal lobe: perilesional and posterior mesial temporal	87	Left language, left memory 4/12, right memory 7/12; bilateral memory impairment with greater dysfunction laterlized to the left
12[a]	*R*	*English*	*Left temporal lobe: posterior superior temporal gyrus, immediately posterior to cavernoma*	*103*	*Left language, left memory 11/12, right memory 8/12; suggestive of right hemispheric memory dysfunction*
13	R	English	Left temporal neocortex and insula	98	Left language, left memory 12/12, right memory 9/12
14[a]	*R*	*English*	*Left hemisphere, multilobar (left temporal, postcentral, frontal, occipital, insula)*	*145*	*Left language, left memory 10/12, right memory 12/12; intact memory bilaterally*
15	L	English	Multifocal (left posterior perisylvian and superior parietal lobe, right anterior perisylvian)	81	NA
16	R	English	left lateral temporal neocortex, superior to the margin of the prior resection	116	Left language, left memory 10/12, right memory 7/12; right hemispheric memory dysfunction
17	R	Mandarin	Left mesial temporal lobe	-	Left language, left memory 6/12, right memory 10/12; left hemispheric memory dysfunction
18	L	English	Broad left frontal-temporal focus	114	NA
19	L/R	English; Turkish	Left occipital cortex	89	NA
20	L	English	Left multilobar	low	NA

[a]Four patients (6, 10, 12, 14) were excluded from analyses following data clean-up. These patients' data are marked with italics.
[b]The Wechsler Verbal Comprehension Index (VCI) indicates each patient's ability to apply verbal skills and information to problem solving.

Table 2. Electrode counts from all 274 trials considered in the present analysis

Region	No after-discharges[b]		After-discharges	
	in	out	in	out
Regions of interest[a]				
postcentral	24	24	*3*	*6*
precentral	35	29	*10*	*9*
pars opercularis	9	9	*12*	*20*
pars triangularis	21	16	*10*	*5*
supramarginal	15	47	*4*	*6*
rostral STG	-	-	*8*	*3*
middle STG	17	8	*15*	*14*
caudal STG	29	19	*2*	*6*
rostral MTG	-	-	*1*	*1*
middle MTG	4	4	-	-
caudal MTG	11	9	*7*	*5*
Subtotal	**165**	**165**	*72*	*75*
Other regions				
caudal MFG	*2*	*3*	*1*	*2*
rostral MFG	*4*	*2*	*7*	*3*
superior parietal	-	*1*	-	-
banks superior temporal sulcus	-	-	*7*	*5*
transverse temporal	-	-	*1*	-
inferior temporal	*1*	*1*	-	*2*
middle temporal	-	-	-	-
precentral (depth)	*2*	-	-	-
insula	*3*	-	-	-
left cerebral white matter	*6*	*8*	-	*1*
left pallidum	*1*	-	-	-
left putamen	*1*	-	-	-
unknown	-	*5*	*1*	*1*
Subtotal	*20*	*20*	*17*	*14*
Grand total	***185***	***185***	***89***	***89***

[a]The top section includes trials within the five broad regions of interest, including sensorimotor cortex (postcentral/precentral gyrus), IFG (pars opercularis/triangularis), STG (rostral/middle/caudal), supramarginal gyrus, and MTG (rostral/middle/caudal). Columns showing trials with stimulation in other regions are italicized, as these were not included in the present analyses.
[b]The central section includes trials for which stimulation did not induce afterdischarges. Columns showing trials that did induce afterdischarges are italicized, as these were not included in the present analyses.
STG: superioir temporal gyrus; MTG: middle temporal gyrus; MFG: middle frontal gyrus